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OFFICE OF THE PROVOST AND EXECUTIVE VICE PRESIDENT --
ACADEMIC AND HEALTH AFFAIRS

OFFICE OF THE PRESIDENT
1111 Franklin Street, 12th Floor
Oakland, California 94607-5200

December 1, 2006

Sandra Shewry.
California Department of Health Services
MS 0000
P.O. Box 997413
Sacramento, California 95899

Re: Comments on Proposed Guidelines for Stem Cell Research: Recommended by the Human Stem Cell Research Advisory Committee Pursuant to Health and Safety Code §125118 (http://www.mch.dhs.ca.gov/documents/pdf/RecommendedGuidelines9%2030%20(Revision%204).pdf)

Submitted electronically to: Amber Christiansen at AChristi@dhs.ca.gov

Dear Director Shewry:

I am writing on behalf of the University of California (UC) Office of the President's Office of Research to respond to the California Department of Health Services' (DHS) request for comments relating to the above-referenced *Proposed Guidelines for Stem Cell Research: Recommended by the Human Stem Cell Research Advisory Committee Pursuant to Health and Safety Code §125118.*

UC appreciates the work of the Human Stem Cell Research Advisory Committee that your office convened pursuant to Section 125118.5 of the California Health and Safety Code (enacted by Senate Bill 322) to recommend guidelines for the conduct of research involving the derivation and use of human embryonic stem cells (hESC). We recognize the importance of ensuring that stem cell research is conducted according to high ethical and scientific standards, and appreciate the efforts of the Advisory Committee to draft guidelines that will provide a framework for the ethical and effective conduct of human stem cell research in California.

Described below are a number of comments and suggested changes related to specific sections of the proposed Guidelines. In most instances, we have not provided comments on those sections of the Guidelines that exactly mirror proposed California Institute of Regenerative Medicine (CIRM) Medical and Ethical Standards (MES) that apply to research funded by CIRM through Proposition 71. UC already provided comments to CIRM during the public comment period of that agency's regulatory process, and we will not reprise all our comments here, as we believe our most significant concerns were largely addressed, and as we support the efforts of the Advisory Committee to promote consistency with CIRM's MES. While we understand that the proposed DHS Guidelines would not apply to stem cell research funded by CIRM, and while the CIRM standards apply only to CIRM-funded research, we believe that consistency between the DHS Guidelines and CIRM's Medical and Ethical Standards regulations will reduce potential confusion and facilitate institutions' compliance efforts.

One overall comment we have about the proposed draft issued by the DHS Human Stem Cell Research Advisory Committee is that, contrary to our understanding of what was called for by Senate Bill 322, the draft is written in such a way as to suggest regulations rather than guidelines.

That is, the draft sets out standards for what “shall” “may” and “may not” occur, and even in several places refers to the Guidelines as “regulations” (e.g., Page 6, line 20; Page 9, Line 20; Page 10, line 11; Page 11, line 13; Page 19, line 12; Page 21, line3; Page 23, line 6). While this is understandable since the Guidelines were modeled closely on the CIRM MES regulations, it may be advisable to review the format of the Guidelines and to clarify the intended (non)regulatory status and effect of the document.

Other more specific comments are as follows. The line and page numbers refer to the pagination in the document posted for comment on the DHS website at the url referenced in the subject line of this letter:

Page 3, Line 10
The Preface correctly notes that Federal law requires, in most cases, that an Institutional Review Board (IRB) review research covered by the CIRM regulations and the proposed DHS Guidelines if it involves “human subjects.” The Preface also includes the statement that “Therefore, research involving the derivation or use of human embryonic stem cells…will have to be reviewed and approved by both an SCRO Committee and an IRB.” We believe this statement could lead to the mistaken conclusion that ALL research involving derivation or use of hESCs will require approval by both a Stem Cell Research Oversight (SCRO) committee and an IRB. Institutional Review Boards are charged with reviewing only that research that involves human subjects as defined by federal regulations. In fact, purely *in vitro* research that involves use of previously derived hESCs does not require IRB review under federal law, and our understanding of the proposed CIRM MES and proposed DHS Guidelines is that such research may require notification of but not approval of an SCRO committee. To avoid confusion, we suggest revising the statement in the Preface to refer to “…<u>some</u> research involving the derivation or use of human embryonic stem cells...”

Page 8, Line 9
The term "professional or financial stake" is undefined, and it is unclear whether/how this differs from a conflict of interest. While we understand and support the goal of examining significant non-financial as well as financial interests in determining whether there is a conflict that should preclude participation, the use of the undefined term "professional or financial stake" could lead to confusion. We recommend using the term "conflicting interest," which mirrors both the current federal regulations relating to conflicts of interest and Institutional Review Boards (45 CFR 46.107) and the proposed CIRM Medical and Ethical Standards. Because institutions are familiar with implementing conflict of interest rules using this term, its use in the DHS guidelines would facilitate institutional efforts to comply with this section. We therefore recommend deleting the term "professional or financial stake."

Page 8, Line 6-7
The requirement that an SCRO committee include at least one patient advocate was already included in Line 3, and so can be eliminated in Lines 6 – 7.

Page 9, Line 17
This requirement should be revised to refer to "<u>a</u> member" rather than "<u>the</u> member" with expertise in assisted reproduction. This would make the requirement consistent with CIRM standards, and reflects the fact that members of Stem Cell Research Oversight committees may have more than one area of expertise (and would avoid implying that SCRO committees must

allot one membership "slot" for an assisted reproduction expert, another for a developmental biologist, etc.). It would also mirror language used in Section 5(a).

Page 10, Lines 22-23
We recommend replacing "confidentiality of the donor(s) is protected" with "the privacy of the donor is protected and the confidentiality of identifiable information is maintained" to more closely mirror federal regulations.

Page 12, Lines 2-5
Our understanding is that this language regarding review of SCRO Committee decisions mirrors an earlier (and now revised) version of CIRM's *Medical and Ethical Standards*. This language has now been removed from CIRM's MES and replaced with the language immediately following (beginning "In cases where..."). To promote consistency with both CIRM regulations regarding SCRO committee decisions and existing federal policy relating to IRB decisions, we recommend deletion of Lines 2 – 5.

Page 14, Lines 8-19.
As currently structured, there are two sections of the Guidelines that set out provisions applicable to procurement of oocytes – Section 7(b) (Page 14, lines 8 – 19) and Section 8 (Page 14, line 20 through Page 16, line 7). There is some overlap and redundancy in the language of these two sections. For example, both sections contain provisions specifying that the physician attending an oocyte donor should not be the principal investigator except in exceptional circumstances approved by an IRB, and that the physician performing oocyte retrieval should not have a financial interest in the outcome of the research. Our understanding is that the provisions in Section 8 are meant to apply to <u>all</u> covered stem cell research involving procurement of oocytes, while Section 7(b) is meant to set out provisions applicable only to a subset of such research (research involving <u>derivation</u> of new human stem cell lines). It may prove less potentially confusing to re-order these sections, placing the provisions that apply to ALL covered stem cell research involving oocytes first, followed by a section that includes only those additional provisions thought to be needed for research involving derivation of new human stem cell lines. Our understanding is that the provisions currently in Section 7(b) and not repeated in Section 8 are, indeed, meant to apply only to research involving derivation, but the Committee may wish to review the placement of provisions to avoid any confusion as to the scope and applicability of the two sections.

Page 14, Line 11
We recommend inserting "knowingly" before "compromise" ["…research shall not <u>knowingly</u> compromise the optimal reproductive success of the woman in infertility treatment…"] to promote consistency with proposed CIRM regulations.

Page 14, Lines 13-14
The wording of the provision in Section 7 of the Guidelines, regarding costs of medical care required as a direct and proximate cause of donation of oocytes for research, is inconsistent with that of the provision in Section 8 on the same topic, and appears potentially problematic. While we support the goal of ensuring that research subjects have access to medical care for research-related injuries at no cost to themselves, we believe institutions should be able to look to commercial sponsors to cover such costs when appropriate. We are concerned that as currently written, this provision might prevent institutions from requiring that commercial sponsors of research assume the costs of medical care subjects may require as a direct result of participating

in a sponsor's research protocol. A number of institutions, like the University of California, require commercial sponsors to assume the costs of subject injuries that may occur in the course of industry-sponsored research protocols. A provision in state guidelines or regulation requiring that institutions themselves assume such costs might compromise the ability of institutions to successfully negotiate with commercial sponsors to require sponsors to pay for such costs. We raised this issue in commenting on the draft CIRM MES regulations, and the provision that is currently on the CIRM regulations took this concern into account. The wording of the CIRM provision is very similar to the wording of Section 8(c) of the proposed DHS Guidelines.

Because Section 8(c) of the draft DHS Guidelines already contains a provision that would apply to <u>all</u> covered research involving procurement of oocytes (i.e., not just to procurement related to derivation of new stem cell lines, as Section 7(b)(2) would), because the language of Section 8(c) protects subjects in a way consistent with the CIRM regulations, and because of the concern outlined above, we recommend deleting Section 7(b)(2) on Page 14, Lines 13-14.

Section 9: Pages 16-18
The inclusion of Section 9: *Additional Requirements for Covered Research Involving Clinical Trials* represents a marked difference from CIRM *Medical and Ethical Standards* and National Academy of Science *Guidelines for Human Embryonic Stem Cell Research*. Neither CIRM nor the NAS provide extensive guidance on clinical trials involving human stem cells and we appreciate the efforts of the Advisory Committee to ensure that consideration is given to this important area.

Given that there is little precedent in conducting clinical trials involving human embryonic stem cells, it is critical that any guidance related to such trials be as clear as possible. To this end, we recommend providing a definition of the term "clinical trial" in Section 2: *Definitions*. While it is likely that institutions and their Institutional Review Boards already have a working understanding of the term, providing a definition within the context of the DHS Guidelines for stem cell research would more clearly indicate the scope and applicability of Section 9.

We would also draw attention to the need to give careful consideration to the delineation of functions between SCRO committees and IRBs. A number of the areas of responsibility assigned to the SCRO committee in Section 9 (e.g., Section 9(a)(3)(F), (G), and (H), ensuring that proposals provide justifications related to risks and benefits, ensuring that proposals adequately address diversity issues) may overlap with the traditional role of the IRB. In order to avoid unnecessarily duplicative reviews and promote efficiency while still ensuring that there is adequate oversight of the research and protection of research subjects, institutions should retain the flexibility to assign responsibility for certain aspects of review to whichever institutional body is best equipped to carry out the task. Cooperation and good communication between SCRO committees and IRBs will undoubtedly be important in review of clinical trials involving use of hESCs. Such cooperation may obviate the need for both bodies to separately require investigators to provide certain kinds of information/justifications, and we would hope that the requirements of Section 9 are not meant to suggest the need for separate and duplicative review requirements..

Page 18, Line 2
We recommend replacing "involved" with "that involve".

Page 21, Lines 2-3
The reference to "subdivision (a) of this regulation" is unclear. We advise providing clarification about which provision involving "foreseeable risk" is being referenced.

Page 22, Line 22 through Page 23, Line 9
Section 11, pertaining to "Record Keeping," appears to have been modeled on an earlier (and now revised) version of CIRM's *Medical and Ethical Standards*. The revised CIRM regulations reduce the number of specified data elements that must be kept, presumably in part to reduce burden on institutions. We recommend reviewing the revised CIRM standard [http://www.cirm.ca.gov/laws/pdf/npoc_mes_regs.pdf], and revising the proposed DHS Guidelines accordingly.

Thank you for the opportunity to comment on the proposed draft Guidelines on Stem Cell Research. We appreciate DHS' efforts to seek public comments. Please do not hesitate to contact me with any questions you may have.

Sincerely,

\s\

Ellen R. Auriti
Executive Director
Research Policy and Legislation
University of California, Office of the President

Copy: Provost and Executive Vice President Hume
Vice Provost Coleman
Professor Henry Greely, Stanford University (Advisory Committee Chair)